

The Argentinian Society of Osteology and Mineral Metabolism (AAOMM) is a national scientific society founded in 1984 dedicated to clinical and basic research into mineralized tissue. AAOMM Meetings are held annually, attracting a wide audience from throughout Argentina, Latin America, and beyond. The program brought together world leaders such as Dr John Bilezikian, Dr Teresita Bellido, Dr Luis del Río, and Dr Isidro Salusky.

The sessions this year were:

ASBMR 2019 highlights

Glucocorticoids: bone and muscle effects

Chronic hypoparathyroidism

Hyperparathyroidism

Bisphosphonates, 50 years of history

Sequential treatment for osteoporosis

Osteoimmunology

Secondary osteoporosis

Rare bone diseases

Treatments for bone diseases: an update

Vertebral fractures

Densitometry in pediatrics

Regenerative Medicine

Fifty-eight abstracts were submitted and presented at the meeting, and 27 of them are listed here:

Preliminary study of assessment of cortical and trabecular bone in patients with Gaucher disease due to 3D reconstruction of the proximal femoral due to DXA

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Objective: Evaluate cortical and trabecular bone in patients with Gaucher disease (GD) treated with imiglucerase and its relationship with bone mass and vertebral fractures. They were compared with it will be evaluated with a control group. **Materials and methods:** an observational descriptive study of 73 patients with EG over 18 years of both sexes treated with imiglucerase were evaluated. BMD on lumbar spine and femoral neck by DXA (Lunar Prodigy Advance) were performed. Dorsal and lumbar spine Rx were used to assess the presence of vertebral fractures. The 3D analysis of the proximal femur was performed with the 3D-Shaper software (Galgo Medical, Spain). The following variables were considered: integral volumetric BMD, trabecular volumetric BMD, cortical BMD (sdens). The data are expressed as mean \pm SD and the differences were considered significant if $p < 0.05$. The Student t-test or the Mann-Whitney test were used. **Results:** 73 patients with GD (34.5 \pm 13.3 years and 11.5 years of diagnosis of GD), 56% women. All patients had received imiglucerase (mean dose 52 \pm 15 U/kg). The lumbar spine BMD (L1-L4) was 1.151 \pm 0.148 g/cm² while in the femoral neck it was 1.021 \pm 0.18 g/cm². BMD was normal in 80% of subjects while osteopenia or osteoporosis was found in 20% of patients. The 3D hip analysis yielded the following results: cortical sdens = 164.7 \pm 27.3 g/cm²; trabecular volumetric BMD = 216.6 \pm 52.1 g/cm³; integral volumetric BMD = 364.5 \pm 60.6 g/cm³. 13.4% of subjects with vertebral fractures were found. No significant differences were found between fractured and non-fractured, with BMD of the lumbar spine and femoral neck. The analysis of the cortical and trabecular components through 3D reconstruction of the proximal femur also showed no significant differences between patients with and without vertebral fracture. **Conclusion:** In our preliminary study we found no differences in the cortical and trabecular bone of the hip in patients with vertebral fractures and also with BMD. This is the first report of bone structure and size analysis in patients with Gaucher disease.

Sequential treatment for idiopathic osteoporosis in premenopausal women. A case report

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Idiopathic osteoporosis (IOP) affects young, otherwise healthy individuals with intact gonadal function and no secondary cause for bone loss or fragility. IOP may be associated with major osteoporotic fractures such as low-trauma spine or hip. **Aim:** To evaluate the safety and effectiveness of sequential treatment in premenopausal women diagnosed with IOP. **Case presentation:** A 33-year-old premenopausal woman was referred by the Gynecology Department to evaluate bone and mineral metabolism. At 28 years of age, the patient had shown a fracture for bone fragility on her right hip. Attaining menarche at age 9, she had regular menstrual cycles (estradiol: 39.3 pg/ml and follicle-stimulating hormone: 8.4 mIU/l). At the time of consultation, she showed a bone mineral density (BMD, Hologic Discovery Wi) in lumbar spine: 0.720 g/cm²; Z-score: -3.2, and in total left femur: 0.536 g/cm²; Z-score: -3.3. No osteoporosis-provoking secondary causes were identified; thus, it was interpreted as IOP. She received sequential therapy (ST) with teriparatide (PTH1-34; Forteo, USA) for two years, and then with densomab 60 mg s.c. (Prolia; USA) associated with a calcium dietary supply of 1000 mg/day and vitamin D₃ 100.000IU/bi-monthly. **Results:** A 19% increase in LS BMD (least significant change [LSC]: 2.2%) and 16% in FIT (LSC: 3.0%) were observed. **Conclusion:** The ST was associated with large increase in BMD of LS and FIT in our patient. No adverse effects associated with teriparatide or densomab were observed. Further clinical studies are necessary to determine the safety and effectiveness of ST in those premenopausal women with IOP. Until then, ST should be used with caution.

Curcumin supplementation may attenuate the development of metabolic alterations associated with the consumption of a fat-rich diet

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Epidemiology shows that Argentinean diet is high in calories, saturated fats and cholesterol and is associated with the development of metabolic diseases, obesity, CVD, hepatopathies and osteopathies. Instead, there is an interest in natural dietary supplements. Curcumin (CUR) has been related to inflammatory attenuation, fat oxidation, antioxidant enzymes-expression and cardiovascular improvement. However, CUR effects in health have not been elucidated yet. Objective: to investigate the effectiveness of CUR supplementation in the prevention of metabolic disorders caused by the consumption of high fats and cholesterol diets. Methods: Wistar rats were assigned in groups: 1. Control (C): fed pellets. 2. High fat diet (HFD), and 3. HFD+CUR, supplemented with CUR (20 mg/day orally). Diet was administered during 5 weeks. Then, rats were euthanized and metabolic parameters were evaluated: lipid profile (mg/dl); visceral fat (%; gravimetry); 2',7'-Dichlorodihydrofluorescein-diacetate [(DCFH-DA(U.A./min.mg prot)]; hepatic steatosis (staining H&E); bone structural properties [(BSP), three-point bending test. Instron 4442]. Results: (ANOVA-SNK, $p < 0.05$). HFD produces hypercholesterolemia ($p < 0.001$) without differences with HFD+CUR ($p > 0.05$). HFD+CUR, prevented body weight and visceral fat gain shown in HFD ($p < 0.05$). HFD showed grade 3 hepatosteatosis, but HFD+CUR did not exhibit inflammatory infiltrate. The supplementation with CUR reduces DCFH-DA ($p < 0.001$). In BSP, there was a significant reduction of the resistance to fracture in animals HF ($p < 0.01$), showing a lower bone quality. Instead, HFD+CUR improved the bone stiffness ($p < 0.001$). CUR could not totally reverse the damage caused by HFD. However, the results suggest an anti-adipogenic potential, related to oxidative stress, inflammation, and resistance to fracture, demonstrating a possible protective effect of CUR.

Bone alterations in the experimental metabolic syndrome: effect of a natural antioxidant

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There is considerable evidence that a fructose rich diet (FRD) causes adverse metabolic perturbations. The aim of this study was to know the effect of naringin (NAR) on bone alterations in FRD rats. Wistar male rats were used: 1) controls, 2) FRD: the same control diet plus 10% fructose, 3) FRD treated with 40 mg NAR/kg b.w. for 30 days. The data showed that serum osteocalcin (OCN) levels were reduced by FRD, and NAR treatment normalized them. FRD rats presented reduced bone mineral density (BMD), bone volume, thickness and intertrabecular spaces. All these changes were blocked by NAR. In distal femur, NAR increased the number of trabeculae. An increase in the number of adipocytes in tibiae from FRD rats was avoided by NAR. In the proximal tibiae from FRD rats, the number of OCN(+) cells and osteocytes decreased as compared to that of control rats. NAR treatment increased the number of OCN(+) cells and osteocytes. The GSH content in bone marrow of femur from FRD rats was similar to that of the control rats, but NAR treatment increased total GSH in comparison with that from the control and FRD rats. $\cdot O_2^-$ levels were highly augmented by the FRD and NAR could not normalize them. CAT activity decreased in FRD rats and NAR administration blocked this response. NAR increased the BMD from cortical and trabecular femur of FRD. In summary, NAR avoids the bone alterations

triggered by FRD. The BMD and OCN normalization, the reduction in the number of adipocytes and the increase in the number of osteocytes suggest that NAR is acting as a possible bone protector in metabolic syndrome.

Antineoplastic effect of the flavonoid quercetin in a Kaposi's sarcoma cellular model

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Quercetin (QUE) is a flavonoid present in a wide variety of foods with different biological and pharmacological effects such as antitumor activity. Kaposi's sarcoma (KS) is a malignant Herpesvirus-induced tumor characterized by angiogenesis and proliferation of cells with characteristics of activated endothelial cells. In this work we studied the antineoplastic effect of QUE and the modulation of ERK1/2, AKT and Wnt/ β -catenin signaling in a KS cellular model. Tumor cells were treated with QUE at different concentrations (1-50 μ M) for 24 and 48 h. Crystal violet staining revealed that QUE significantly decreases cell proliferation in a dose and time dependent manner: $77.8 \pm 5.1\%$ 20 μ M vs. C and $85.7 \pm 7.5\%$ 50 μ M vs. C (24 h); $66.4 \pm 6.3\%$ 10 μ M vs. C, $55.9 \pm 2\%$ 20 μ M vs. C and $50.8 \pm 7.3\%$ 50 μ M vs. C (48 h). In concordance, representative images showed an increase of cells with apoptotic characteristics. MTS assay demonstrated a significant decrease in cell viability at highest doses of QUE ($84.4 \pm 7.1\%$ 20 μ M vs. C; $86 \pm 6.9\%$ 50 μ M vs. C) at 24 h and ($63.7 \pm 7\%$ 10 μ M vs. C; $43.3 \pm 5.7\%$ 20 μ M vs. C; $34.3 \pm 7\%$ vs. C) 48 h. Under the same experimental conditions, phosphorylated ERK1/2 and AKT were analyzed by Western blot (WB) revealing an increment in their phosphorylation levels in a dose dependent way after 24 h of QUE. Since Wnt/ β -catenin signaling pathway play an important role in tumor development and is activated in KS, β -catenin protein levels were also analyzed by WB showing an increment of its expression from 5 μ M of QUE. Altogether, these results demonstrate an antitumor effect of QUE on KS cellular model, accompanied by ERK1/2 and AKT activation and an increase in β -catenin expression, a key protein of Wnt signaling pathway.

Densitometric and geometric differences in distinct types of hip fractures

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Hip fractures are multifactorial. Mechanical competence of the hip is one of these factors. It is the result of the interaction of multiple properties such as size, shape and geometry. Purpose: to assess whether there are differences in bone densitometry (BMD) and geometric properties among women who experienced a cervical (CF) or transtrochanteric (TTF) hip fracture (HF), compared to those without a fracture. Methods: we included 46 female patients with HF between 2015 and 2018 and a BMD measured by DXA within the previous 5 years and 40 controls of the same age randomly selected. We analyzed: age, T-score of total hip, femoral neck (FN) and Ward's triangle, FN area, hip shaft length and cervical-diaphyseal (c-d A) angle. We calculated the "robustness" of the hip: average width FN (neck area/1.5 cm) / length of the hip axis, being informed as robust or slender. Statistics: Student's t- test for cases and controls, non-parametric test: Kruskal-Wallis and Mann-Whitney for differences between groups, Chi square for difference in proportions. Results: patients with HF have lower BMD in FN, total hip and Ward's triangle ($p < 0.001$). They also have a longer length of the hip axis ($p = 0.042$) and greater c-d A angle ($p = 0.07$). BMD decreased as follows: controls $>$ TTF $>$ CF ($p = 0.006$). Ward's triangle in TTF is lower than in controls and CF, in CF it is similar to controls. T-score ≤ -2.5 was

observed in 20% in controls, 32% of CF and 66% of TTF (chi-square = 0.0023). CF have more open c-dangle ($p=0.039$), longer hip axis length ($p=0.06$) and lower neck robustness (more slender) than controls ($p=0.046$). FTT are similar to controls. The age of the FTT group is greater than that of the FC group. Conclusion: women who suffered TTF fractures are older and have lower BMD, as classic osteoporotic fractures. Those with CF do not have BMD in osteoporotic range, but they have different geometric parameters to controls: greater cervical-diaphyseal angle, more slender femoral neck and longer hip axis length.

Patients with fractures of both hips tend to repeat the type of fracture

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Introduction: approximately 10% of patients who suffered a hip fracture (HF) have a new event in the contralateral hip in the next 5 to 10 years. The aim of the study was to assess the coincidence of the type of fracture, cervical (CF) or transtrochanteric (TTF), in patients who suffered a fracture of both hips. Methods: we retrospectively evaluated patients with hip fracture treated at our institution between 2015 and 2019. A total of 22 patients who suffered previously a contralateral hip fracture were identified. Images were available in 18 cases, in the remaining 4, we considered valid the radiological report and/or clinical history. Images evaluation and classification of the type of fracture were carried out blindly by 2 orthopedists, who agreed 100%. Statistics: the proportion of coincident fractures in type and their confidence interval (for a single proportion) was calculated. In addition, median interval between both fractures was determined in months. Results: 18 of 22 patients had the same type of fracture, proportion $p=0.812$, CI (95%): 0.657-0.979, $p=0.0014$ (z statistic, rejects the hypothesis of nullity of proportion = 0.5). We observed the following sequences: 9 TTF/TTF, 9 CF/CF, 2 TTF/CF and 2 CF/TTF. The median interval between fractures was 19.5 months (range: 3-118 months). The median age of the first fracture was 83.5 years (range: 68-91 years) and the median age of the second fracture was 87 years (range: 73-95 years). There were no differences in the age of the different fracture sequences. Conclusion: patients who suffer two hip fractures tend to repeat the same type, what means that they do not occur stochastically. This would suggest that they have certain predisposing characteristics for the repetition of the type of fracture, related to the mechanical competence of the hip and / or the configuration of the fall.

Effects of fructose-induced metabolic syndrome and long-term metformin treatment on bone microarchitecture and biomechanics

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Metabolic syndrome (MS) in rats decreases the osteogenic potential of bone marrow stromal cells (BMSC), and this can be prevented by oral metformin (MET). However, long-term MET treatment of rats without MS may affect BMSC increasing their RANKL/OPG ratio. Here we evaluate long-term effects of MS and/or MET on bone microarchitecture and biomechanics. 46 young male Wistar rats were allocated (n=8-10) to: B (Baseline); C (Control, drinking water); F (20% Fructose in drinking water); M (100 mg/kg/day MET in drinking water); and FM (Fructose+MET in drinking water). Except B,

all treatments were continued for 3 months. Double fluorochrome labelling and blood sampling was performed before sacrifice. We dissected: tibiae and 2nd lumbar vertebrae for static and dynamic histomorphometry and pQCT; femora for mechanical tests. Group F (vs C) increased glycemia and triglyceridemia, which was prevented by MET (group FM). No significant differences were found between groups F and C for any bone parameter evaluated. All MET-treated animals (groups M and FM) showed alterations in the tibiae versus group C: significant decreases in trabecular BV/TV, Tb area, Tb.Th, total and trabecular BMC, and trabecular BMD; and a significant increase in Tb.Sp and trabecular eroded surface. No differences between groups were found for dynamic histomorphometry or biomechanics. Our model of MS in rats does not induce long-term bone alterations. Long-term MET treatment (in the presence or absence of MS) alters appendicular trabecular bone microarchitecture (possibly due to an increase in trabecular resorption) but not biomechanical properties.

Poly-L-Lactic in regenerative medicine

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Biodegradable synthetic polymers represent an important group within the materials used for regenerative biomedical application. We previously synthesized a poly-L-Lactic scaffold using ring opening polymerization of the cyclic dimer (PLLA), which did not possess cytotoxic effects in cell cultures and had lower production costs. Our aim was to verify if this scaffold is useful in bone tissue engineering under in vivo conditions (N: New Zealand female rabbits). 15 N (4 months) were randomly divided into Groups A, B and C (control) (n=5). A and B were subjected to 6 mm diameter osteo-femoral lesion, and A rabbits were implanted with PLLA at the site of the lesion. An adequate clinical condition and gait was shown in A and B from day 5 on. No differences in biochemical values (hemograms and transaminases) were detected after 1, 5 and 90 days. In A rabbits, both conserved cortices were observed, with continuity. Tomography showed higher calcified areas in A than in B. Material compatible with PPLA was detected on day 90, surrounded by a thick layer of neoformed composite bone. Inside the material there were moderate trabeculae with osteoblast-like cells. Although preliminary, our data show that PLLA did not cause rejection, and promoted incipient tissue neoregeneration. Since the PLLA has strength, flexibility and malleability properties, it would have potential application for the development of screws and other types of implants in which it is necessary to repair an injury, without undesirable side effects. PLLA is a promising 3D material to be used in regenerative medicine

Evaluation of a yogurt with galactooligosaccharides (GOS) obtained by lactose fermentation, as a tool to ensure bone health in intolerant individuals

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GOS, natural prebiotics of human milk could be incorporated in dairy products, such as yogurt, by enzymatic action on milk lactose. The functional characteristics of such reduced-lactose yogurt containing GOS were previously demonstrated in normal growing rats. Objective: To evaluate the

beneficial effects of this reduced-lactose yogurt containing GOS in Ca and P absorption and bone retention. Male weaning Wistar rats (n=10 per group) received during 30 days AIN'93-G control diet (CD) or the yogurt containing GOS diet (ED). Ca and P Abs were evaluated during the last 3 days of the experience; depth of intestinal crypts, femur Ca and P content, bone mineral content (BMC) and bone mineral density (BMD) at the end of the study. BMD of lumbar spine (LS), of total (TT) and proximal (PrT) tibia, and TT BMC were also evaluated. The results (ED vs. CD) were expressed as mean \pm SD. Food consumption and PC were similar in both groups. The %AbsP was significantly higher in group ED (86.6 \pm 6.6 vs. 78.0 \pm 7.1%; $p < 0.05$), and %AbsCa showed a non-significant higher level in group ED (84.9 \pm 2.2 vs. 80.0 \pm 5.4%; $p = 0.062$). TT BMD (0.246 \pm 0.022 vs. 0.246 \pm 0.018 g/cm²), TT BMC (0.029 \pm 0.004 vs. 0.030 \pm 0.014 g), and CL BMD (0.250 \pm 0.017 vs. 0.251 \pm 0.019 g/cm²) no showed significant differences, while BMD TPr (0.303 \pm 0.056 g/cm² vs. 0.266 \pm 0.018; $p < 0.05$) was significantly higher in group ED. The depth of the intestinal crypts was non-significant greater value in group ED (212.59 \pm 12.39 μ m vs. 205.12 \pm 21.27 μ m; $p = 0.28$). Femur Ca and P content showed no significant differences between groups. These results suggest that the assayed here functional product would be an optimal tool to achieve the bone mass peak, preventing future bone alterations, in lactose intolerant individuals.

Changes in proinflammatory mediators involved in bone mechanotransduction modify alveolar post-tooth extraction repair in a rat hyposialia model

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Mechanotransduction (MCT) is the process by which osteocytes (OT) convert physical forces into chemical signals, which are then integrated into a cellular response. Prostaglandins (PG) and nitric oxide (NO), known proinflammatory (PI) molecules, have been studied widely in bone since they are considered important chemical signals in early MCT. Furthermore, PGE2 promotes expression of sclerostin, a key molecular factor in bone MCT. Saliva is a crucial element in oral wound healing; we previously demonstrated that hyposialia affects tissue repair post-tooth extraction. However, little is known about the role of OT in alveolar bone repair. Aim: To study the effect of submandibulectomy (SMx) on alveolar bone repair focusing on PI mediators involved in MCT. Methods: Male Wistar rats aged 21 days (n=48) divided into 2 groups: SMx (SMxG) and Control (CG). Under anesthesia, rats were subjected to SMx; 7 days post-SMx, both groups underwent bilateral extraction of the 1st lower molar. They were fed a soft diet. The rats (n=6) were euthanized at 3-7-14-30 days following the FOUBA CICUAL guide. The tissue was obtained to assess PGE2 levels and iNOS activity. A group of end-point rats (30 d, n=10) was used for histomorphometric and biomechanical evaluation. The data were analyzed by one-way ANOVA. Significance was set at $p < 0.05$. Results: Data CG vs. SMxG are shown as mean \pm SD: PGE2 (pgPG/s) 733.3 \pm 203.2 vs. 1841.2 \pm 646.6 at 3 d and 216.4 \pm 32.2 vs. 309.2 \pm 52.5 at 30 d; NO (pmol NO/min/mg) 21.2 \pm 5.5 vs. 46.1 \pm 22.2 at 3 d and 0.88 \pm 0.8 vs. 2.03 \pm 1.1 at 30 d. Histomorphometry at 30 d revealed: B.Ar/T.Ar (34.8 \pm 3.3 vs. 58.4 \pm 4.9), Ob.Pm (25.3 \pm 1.8 vs. 34.5 \pm 2.6), E.Pm (8.346 \pm 0.78 vs. 13.63 \pm 1.1), N.Ot/mm² (2037 \pm 73.03 vs. 2675 \pm 92.13) N.E.Lc/mm² (117.4 \pm 52.6 vs. 624.7 \pm 59.6). Conclusion: SMx causes changes in PGE2 and NO that could lead to an alteration in MCT during alveolar bone repair, and promote formation of bone with different properties. UBACYT 2018-2020/159BA.

Similar actions of estrone on vascular and bone tissues: ¿Risk or benefit?

Estrogens play an important role in atherogenesis and bone remodelling. We previously reported the osteoblastogenic effect of estrone (E₁). Although E₁ showed a positive action on bone tissue, we have also found negative effects tending to vascular lesions progression. The aim of this work was to compare E₁ effect on osteoblasts (OB) and vascular smooth muscular cells transdifferentiated into osteoblasts (CMLV-OB), particularly in modulation of cell maturation. E₁ increased cell proliferation on both cellular types (27%, 39% above each/C p<0.05, CMLV-OB, OB resp, MTT assay; 28%, 41% above each/C p<0.05, CMLV-OB; OB resp., cell counting). In CMLV-OB, E₁ enhanced ALP activity (3.72±0.25 vs 3.00±0.14; E₁vsC, IU.10⁻²/mg prot, p<0.001, enzymatic assay) and the number and size of calcification nodules in extracellular matrix (56% a/C, p<0.05; alizarin red staining). Concordantly, E₁ decreased calcium content in culture medium (735.0±30.5 vs 468.2±21.1; C vs E₁, µg Ca/mg prot, p<0.001; commercial kit). Indeed E₁ enhanced extracellular collagen deposition in CMLV-OB cells, visualized by Sirius red staining (↑19 % a/C, p<0.05). Similar results were obtained employing native bone cells (OB). E₁ treatment stimulated ALP activity (4.64±0.32 vs. 3.37±0.25; E₁ vs C; IU. 10⁻²/mg prot, p<0.001), calcium deposition (40.2% a/C, p<0.05) and collagen in extracellular matrix (↑21% a/C, p<0.05). Results presented in this work show a similar action of E₁ in both cellular systems. From a biological point of view, the data suggest that physiological relevance is contrasted: a beneficial action at bone level favoring osteoblastogenesis and deleteriousness at vascular homeostasis, promoting vascular calcification.

Body mass index (BMI) effect on total (OCNt) and subcarboxylated osteocalcin (OCNsc) in normoglycemic adult men

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Obesity and osteoporosis affect glucose homeostasis through OCN and leptin, via different mechanisms. We evaluated BMI influence on OCNt and OCNsc in 33 non-diabetic overweight (OW) and obese (OB) adult men having normal glucose (80 to 110 mg/dl) and hemoglobin A1c (HbA1c <5.7%). They were divided by BMI quartiles in OW and type (T) I, II or III obesity. OCNt, OCNsc, leptin, CTX and 25OHD in ng/ml, and insulin in µU/l was determined. Results (OW, OB TI, TII and TIII, respectively) (mean±SD): Leptin (21±19c, 19±11c, 27±11b, 41±22a) increased as BMI increased (p<0.01). Insulin (12.10±3.20b, 12.40±8.80b, 24.20±8.80a, 23.40±4.10a) was higher in OBTII and OBTIII vs. OW and OBTI (p<0.05); OCNt (25.8±15.40a, 18.80±6.70b, 15.30±4.20c, 8.30±4.10d) decreased as BMI increased (p<0.01). OCNsc (3.98±0.73b, 4.49±1.09a, 4.81±1.22a, 4.31±0.59a) was higher in OW than in OB men (p<0.01). Insulin increase and OCNsc decrease were associated with a tendency to glycemia increase, suggesting insulin resistance and certain degree of OCNsc resistance. CTX (355±30a, 313±101b, 318±54b, 344±8b) was lower in SP than in obese men (p<0.01). The lowest 25OHD (21.20±2.40a, 20.70±6.80a, 22.30±7.90a, 16.80±2.80b) was observed in OBTIII, without differences between the three remaining groups. Conclusion: the results presented here evidenced the negative influence of BMI on bone remodeling (OCNt and CTX), which may contributed to glucose homeostasis modification exerted by OCNsc released from bone matrix. Grants from UBACyT and ULAM.

Citric acid coated magnetic nanoparticles for drug delivery targeting: characterization and biocompatibility on vascular and bone systems

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Citric acid coated magnetic nanoparticles (ca-MNP) consist on a magnetite core coated with citric acid molecules. By the application of an external magnetic field, these MNP can be directed to a specific site of the organism through the vascular system. This nanotechnology find promising applications in targeted drug delivery. The citric acid coating confers biocompatibility and acts as platform for the incorporation of biomolecules. Looking forward bone targeting of caMNP, the present work aims to evaluate their vascular and bone biocompatibility. caMNP were obtained by the co-precipitation method employing ferrous and ferric salts in the presence of citric acid. MNPs showed to have a diameter of 260 ± 14 nm and Z potential of -25.7 ± 4.3 mV, being these properties suitable for biomedical applications. Primary cultures of vascular endothelial cells (EC) and osteoblasts (OB) were obtained by explant technique from aorta and calvaria of Wistar rats respectively. Cells were exposed to 1, 10 and 100 $\mu\text{g/ml}$ of MNPs for 48 h and specific cellular processes were evaluated. Cell viability (MTT assay) was assayed in EC and OB. No effect of caMNP was observed below 10 $\mu\text{g/ml}$. 100 $\mu\text{g/ml}$ of MNPs induced a 22% and 16% decrease in EC and OB viability respectively ($p < 0.01$). In EC, nitric oxide (NO) production was evaluated as a marker of endothelial function (Griess reaction). Basal NO production was not affected by caMNP. Acetylcholine induced endothelial production of NO was also corroborated (4.0 ± 0.2 ; 5.8 ± 0.40 ; 5.9 ± 0.3 nmols NO Cont; AC; MNPac+Ac $p < 0.01$). Alkaline phosphatase activity, matrix mineralization and calcification (Alizarin Red) were studied as OB markers. No significant changes were observed in FAL expression kinetics nor in matrix mineralization at the concentrations tested. These results demonstrate caMNP biocompatibility on vascular and bone components, suggesting their potential use for targeted delivery of therapeutic agents.

Hypercalcemia not mediated by PTH associated with the diagnosis of Pneumocystis Jiroveci Pneumonia in kidney transplant patients.

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Pneumocystis Jiroveci Pneumonia (PJP) represents an important cause of morbidity and mortality in transplant patients. Hypercalcemia is a infrequent form of presentation in this disease. We present three female patients with a history of renal transplantation of more than 3 years of evolution, with hypercalcemia during hospitalization. They were under immunosuppressive treatment with meprednisone 4 mg. Two of them received calcitriol and ergocalciferol, and one was treated with calcium carbonate 500 mg daily. They referred asthenia, adinamia and one of them a febrile syndrome. Laboratory: calcemia (case 1: 11.9 mg/dl, case 2: 10.9 mg/dl, case 3: 12.6 mg/dl RV: 8.5-10.5 mg/dl), 25(OH) vitamin D was within the normal range, creatinine clearance was between 12-30 ml/min and PTH levels were ≤ 20 pg/ml in all cases. Hypercalcemia was interpreted as not mediated by PTH. Chest imaging studies showed pulmonary infiltrates (Positron Emission Tomography or Computed Axial Tomography), bronchoalveolar lavage was performed with diagnosis of PJP by polymerase chain reaction. Calcium and vitamin D were suspended and they were treated with

hydration and calcitonin. Targeted antibiotic treatment was initiated (trimethoprim sulfamethoxazole, subsequently rotated to primaquine plus clindamycin due to nephrotoxicity) All patients evolved with normalization of the calcemia within the first 15 days. Measurement of 1,25(OH)₂ vitamin D levels is not available in our hospital. The clinical suspicion of infections associated with PJP or fungal infections in immunocompromised patients with hypercalcemia as an initial manifestation implies a diagnostic challenge.

Aneurysmal bone cysts: A case series

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Aneurysmal bone cysts (ABC) are rare benign skeletal lesions. They most frequently involve metaphysis of long bones, pelvis or spine. They may occur as a primary bone tumor or secondary to preexisting bone lesions (eg: simple bone cyst, fibrous dysplasia, giant cell tumor). They are usually diagnosed in the first two decades of life. Clinically they present with pain, swelling and palpable mass. Spinal lesions may present with back pain or stiffness, neurologic deficits and radicular pain. Treatment goals are to eradicate the lesion, minimize recurrence, relieve pain and avoid functional impairment. Treatment options are surgery, sclerotherapy, selective embolism, cryotherapy, etc. Recently bisphosphonates have been successfully used as definitive treatment. The aim of this presentation is to describe three different cases of this entity. Case 1: A 28-year-old woman presented with rib tumor and local pain. Initial histology showed a fibrohistiocytic lesion with multinucleate giant cells. Given the probability of being a giant cell tumor surgical excision was performed and fibrous dysplasia with ABC was diagnosed. Case 2: a 38-year-old woman with ABC in C7 and axial pain. Selective embolization of the lesion was performed with partial response. Due to its location with potential risk of spinal cord injury, she underwent intravenous ibandronate therapy with symptoms improvement. Case 3: a 34-year-old woman, diagnosis of fibrous dysplasia with secondary ABQ in sixth rib. She had back pain and refused surgery. Intravenous ibandronate was administered with significant pain improvement. Conclusions: ABC are a diagnostic and therapeutic challenge. Considering its symptoms, location, extent, recurrence rate and benign nature, different treatment alternatives may be considered. The use of bisphosphonates could be an encouraging treatment option.

Hypercalcemia associated with Histoplasmosis, about a case

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A 40-year-old male with renal transplantation immunosuppressed with corticosteroids consulted for fever, persistent cough, weight loss and night sweats. He presented serum calcium 12.2 mg/dl (VR: 8.5-10.5), ionized calcium 1.4 mg/dl (VR: 1.00-1.35), parathyroid hormone 44.8 pg/ml (VR: 8.7-77.1), 25(OH) vitamin D 24.9 ng/ml (>30), creatinine 3.40 mg/dl (VR: 0.60-1.30), without symptoms of hypercalcemia. His previously parathyroid hormone and calcium levels were 479 pg/ml and 8.6 mg/dl. Dietary calcium restriction was performed, cholecalciferol was suspended and parenteral hydration was indicated, but serum calcium increased (ionized calcium: 1.66 mmol/l). The transbronchial biopsy confirmed Histoplasma capsulatum and its pathological anatomy reported granulomatous inflammation. Therefore, hypercalcemia mediated by 1,25(OH)₂ vitamin D was suspected, although its determination is not available in our hospital. Hypercalcemia associated with granulomatous disorders is caused by the increase of 1,25(OH)₂ vitamin D as a result of hydroxylation in macrophages of the granuloma through the enzyme alpha 1 hydroxylase, which leads to an increase in intestinal

absorption of calcium and phosphorus. Treatment aimed at the underlying disease with liposomal amphotericin was initiated. On the seventh day he presented normalization of the serum calcium. Hypercalcemia in patients with kidney disease is a challenge. Parathyroid hormone as in the case of our patient may not be completely inhibited. On the other hand, the renal failure can be a contraindication for the use of bisphosphonates and the experience of treatment with denosumab in transplant patients is limited. In our case, the early diagnosis and treatment of the underlying disease allowed the resolution of hypercalcemia without the need of antiresorptive treatment.

Eye inflammation associated with bisphosphonate treatment

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Bisphosphonates (BP) are first-line drugs in the treatment of osteoporosis and other bone diseases. Uveitis is a rare complication associated with their use. We describe 6 patients with ocular inflammation associated with BP treatment. The age range was between 50 and 86 years. Four received BP for osteoporosis and two for oncologic disease. Five patients developed the inflammatory reaction after the first infusion of zoledronate and one patient after pamidronate. The time of presentation of this adverse effect varied between 12 hours and 7 days after infusion. Five patients developed anterior uveitis and one posterior scleritis associated with optic perineuritis. In all cases the engagement was monocular. Three of them had received previous oral BP, without any adverse ocular reaction. One patient who was treated with a second zoledronate infusion repeated a new episode of uveitis. Patients who had anterior uveitis (n=5) resolved with topical corticosteroids. The patient with posterior scleritis and perineuritis required systemic corticotherapy and hospitalization for pain management. All presented favorable evolution with inflammation resolution within four weeks. Discussion: Drug induced uveitis is infrequent (<0.5%). Other more frequent causes include infections and systemic immune-mediated disease. Eye inflammation associated with BP treatment is an uncommon complication, but it should be suspected in patients who have pain, photophobia or red eye after BP application. In our series all the patients had received BP intravenously. The evolution was favorable with the establishment of local or systemic corticotherapy. Early treatment is essential to improve pain and reduce the risk of complications. Multidisciplinary work is necessary for a proper diagnosis and treatment.

Reversible congenital hypoparathyroidism

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Primary hypoparathyroidism is an inappropriate or absent secretion of PTH. In pediatric age it is usually idiopathic or genetic. Most of them are permanent, but reversible entities have been documented. Case: A 22-year-old woman, born at term, to non consanguineous parents, with normal weight and height, presented, at 3 months of age, seizures associated with fever. Ultrasound showed basal ganglia calcifications. She had multiple hospitalizations due to infectious conditions up to 14 months. At the age of 3 she presented tetany with hypocalcemia, hypomagnesemia, normal phosphorus and PTH 5 pg/ml, microcephaly, hypotelorism, enoftalmos, delayed teething, tapered fingers and short stature. Growth hormone (GH) stimulation test was normal. Echocardiogram, renal ultrasound and T lymphocytes were normal. X-ray showed cortical thickening of long bones. She was

diagnosed with primary hypoparathyroidism. She started substitution with calcitriol, calcium, magnesium (Mg) and vitamin D. She had normal maturational development and intelligence for her age. At the age of 9 she started treatment with GH until age of 14 with suboptimal response. Spontaneous menarche. Prior to the consultation, while receiving calcitriol, she presented phosphatemia 3.1 (2.5-4.5 mg/dl), calcemia 11.2 (8.5-10.5 mg/dl), magnesemia 0.8 (1.9- 2.5 mEq/l), PTH <3 (16-77.1 pg/ml), calciuria 143 (<250 mg/day), fractional excretion of Mg 19 (3-5%). Calcitriol was discontinued and Mg started, which corrected calcemia and raised PTH to 23.3 pg/ml. Genetic panel of hypoparathyroidism with deletion and duplication search was requested. Commentary: A small percentage of hypoparathyroidism diagnosed in pediatric age can be reversible, so follow-up is important. The role of Mg in the regulation of PTH secretion is highlighted, being a determinant in this case, thereby restoring parathyroid functionality.

Chronic treatment of hypercalcemia caused by methacrylate-induced granulomas

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Granulomatous diseases can produce hypercalcemia mediated by 1,25(OH)₂ vitamin D due to increased activity of 1 α -hydroxylase. In recent years, granulomatosis has been reported as reaction to foreign body after the use of methacrylate for aesthetic purposes. Corticosteroids are a first-line therapy in granulomatosis and antiresorptive drugs are part of the usual treatment of hypercalcemia. Other proposed therapeutic options are hydroxychloroquine, ketoconazole and anti TNF alpha antibodies. The purpose of this presentation is to communicate the long-term treatment of a patient with granulomas induced by methacrylate and hypercalcemia of difficult management. Case report: A 43-year-old woman consulted in 2014 with hypercalcemia, lithiasis and renal failure. She had previous injection of methacrylate in lower limbs for aesthetic purposes. Laboratory tests: hypercalcemia 13 mg/dl (VR 8.5-10.5), PTH <3 pg/ml (VR 8.7-77.1), 1,25(OH)₂ vitamin D 180 pg/ml (VR 18-60). PET-CT: hypermetabolic nodular images in both buttocks and thighs. Biopsy: subcutaneous granulomas. She received treatment with hydration, corticotherapy, bisphosphonates and hydroxychloroquine which was suspended due to intolerance. Ketoconazole 400 mg/day was initiated combined with meprednisone 6 mg/day and alendronate 70 mg/week with decrease in serum calcium (9.6 mg/dl) and improvement of renal function (creatinine at 1.49 mg/dl). Conclusions: Treatment of granuloma-induced hypercalcemia associated with methacrylate application is a challenge. The combination of low doses of corticosteroids, ketoconazole and alendronate was an effective therapy in our patient.

Voriconazol-induced periostitis

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Drug-induced periostitis is a recognized entity. Voriconazole is a triazole antifungal agent used in prophylaxis and treatment of fungal infections. There is recent evidence that prolonged therapy with voriconazole may cause diffuse periostitis. Clinical case: A 42-year-old woman diagnosed with acute myeloid leukemia in June 2017, bone marrow transplant in December 2017, graft-versus-host disease and mycosis by *Scedosporium apiospermum* began with arthralgias in hands and generalized bone pain after 9 months of treatment with voriconazole. Physical examination showed swelling and nodular lesions in both hands and relative functional impotence. Bone scan revealed morphological changes at

phalanges and metacarpus and severe periosteal reaction along with increased soft tissue. Laboratory showed increased levels of bone remodeling markers and 24-hour urine fluoride 17.22 mg/l (<3 mg/l). Positron emission tomography determined hypermetabolic periosteal lesions of exophytic growth towards soft tissues in multiple axial and appendicular bone structures. Findings were compatible with extensive periostitis. Bone pain resolved few days after voriconazol discontinuation and radiographic abnormalities decreased. Discussion: Voriconazole-induced periostitis has been recently described. Fluoride included in voriconazole molecule may cause elevated fluoride levels and increased osteoblastic activity with periosteal lesions. The history of multifocal and asymmetric bone pain and imaging evidence of diffuse periosteal reaction in the context of chronic treatment with voriconazole suggested the diagnosis. Increased fluoride levels has diagnostic utility in this entity. Although the suspension of therapy usually achieves rapid symptomatic improvement in 2 to 21 days, as in the case of our patient, radiological alterations may persist for years.

Recurrence of secondary hyperparathyroidism in dialysis patients after parathyroidectomy

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Parathyroidectomy (PTX) is an effective therapy for refractory secondary hyperparathyroidism (sHPT). Continued dialysis exposes patients to developing recurrent sHPT. The aim of this study was to estimate the proportion of recurrence and its predictors. We conducted a retrospective observational study of 92 adults in chronic dialysis, who underwent the first PTX in this centre between 2006 and 2015. We considered persistence of sHPT if PTH was > 300 pg/ml during the first postoperative semester, and recurrence if it was > 500 pg/ml after that. Results: Age 43.6±12 y/o, 50% male, 4.6 years on dialysis, median preoperative PTH 1636 pg/ml (IQR 1226-2098). Subtotal PTX (S-PTX) was performed in 39, total with autotransplantation (TA-PTX) in 53. Persistence of sHPT occurred in 16 patients; relapse in 30 out of 76 initially ameliorated (39.5%; 95CI 28.5-50.5). Median time to recurrence 4.7 y. Recurring patients had higher preoperative calcemia (9.9 vs 9.3 mg/dl; adj OR 2.79) and lower elevation of postoperative ALP (333 vs 436 UI/ml; adj OR 0.99). Recurrence presented more frequently in TA-PTX (48.9%; adj OR 4.66) than S-PTX (25.8%). Conclusions: Time on dialysis with inadequate metabolic control remains the most important risk factor for sHPT recurrence. Higher preoperative levels of calcemia, related to sHPT severity, are associated with recurrence. Lower elevations of ALP during postoperative period in recurring patients are an interesting finding. We hypothesize that patients with less significant postoperative mineralization may have chronically higher levels of phosphatemia, stimulating parathyroid glands. Fewer recurrence in s-PTX is associated to bias in the procedure selection.

Persistent hypophosphatasemia and its musculoskeletal repercussion

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Low alkaline phosphatase (ALP) or hypophosphatasemia (hypoALP) due to hypophosphatasia or secondary causes; although rare, could have clinical implication. The objective is to estimate the prevalence and describe the clinical findings in adults with persistent hypoALP. Methods: A search of electronic medical records of HIBA adult affiliates between 2013 and 2017 was made. Cases with ≥ 2 ALP ≤ 30 IU/l, no ALP > 30 IU/l and without diagnosed secondary causes were analyzed. Results:

Persistent hypoALP was detected in 0.07% (0.06-0.09) of 105925 HIBA members. One patient had celiac disease as a secondary cause, 77 cases were included; 61.1% women, 44 (34-56) years old, ALP 24 (20-27) IU/l and phosphatemia 4.1 (3.8-4.6) mg/dl. Osteoarthritis, vascular calcifications and fractures were observed in 45, 13 and 12 patients respectively, and nephrolithiasis, DISH, tooth loss and seizures less frequently. At least one of the mentioned characteristics was observed in 63.6%, but only 5.2% had hypoALP registered in their clinical record. Densitometry showed osteopenia or osteoporosis in 76.2%. There were 19 fractures, most of them in radius, with no gender predominance. Four patients received bisphosphonates, with low ALP before starting them. Although no atypical fracture was observed, one patient presented multiple fractures (pelvis, olecranon and wrist) after antiresorptive treatment. Conclusions: The prevalence of hypoALP was 0.07%. Recognition in medical records was low, but far from being asymptomatic, varied clinical manifestations were observed. In the presence of hypoALP without a secondary cause, adult hypophosphatasia should be suspected. An adequate diagnosis of hypophosphatasia is relevant due to its clinical and therapeutical implications (antiresorptives should be avoided) and for genetic counseling.

Is sarcopenia a risk factor for rotator cuff tears?

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Sarcopenia is the loss of muscle mass and consequent loss of muscle function with aging. Its prevalence can reach up to 24% in the population over 65 years. Currently, it is considered an independent risk factor for falls and fractures, disability, postoperative complications, and mortality. Rotator cuff tears are known to be influenced by systemic diseases such as diabetes mellitus, hypercholesterolemia, thyroid disease, and osteoporosis. This study aimed to evaluate the prevalence of sarcopenia in patients with and without rotator cuff tears to determine if it can be considered a risk factor for this condition. Methods: This is a prospective case-control study. We evaluated 106 consecutive patients and divided into two groups: Group 1 (cases) included 53 patients with chronic symptomatic full-thickness rotator cuff tears (mean age, 72±5 years), and group 2 (controls) included 53 age- and sex-matched patients (mean age, 71±6 years). The sarcopenic index was evaluated using the grip strength of the dominant side. A gait speed test was performed, and skeletal muscle mass was evaluated with dual energy X-ray absorptiometry (DXA). Rotator cuff pathology was evaluated with MRI in all patients. Results: No significant differences were found in baseline data and demographic factors between the groups, except for the smoking habit ($p=0.02$). The prevalence of sarcopenia was not significantly different between the groups, nor were gait speed, grip strength, and skeletal muscle mass index ($p=0.15$, 0.99 , and 0.9 , respectively). Conclusion: The prevalence of sarcopenia in patients with rotator cuff tears was similar compared with an age- and sex-matched control population. Thus, with these results, we are not able to consider sarcopenia as an independent risk factor for rotator cuff tears.

Post-implant biocompatibility of electro-spun polycaprolactone nanocomposite fibrous scaffolds

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Tissue engineering aims regenerating de novo lost tissue. Our objective was to analyze the biocompatibility of the implant of PCL-nHAp, an electro-spun scaffold prepared by mixtures of a biocompatible and bioabsorbable polyester, poly(caprolactone), and a bioactive ceramic of nanofibrous structure (nanohydroxyapatite particles), in an in vivo model (New Zealand female rabbits). Scaffolds were 5 mm diameter PCL-nHAp discs, superficially modified to increase hydrophilicity by alkaline treatment and sterilized (peracetic acid). Treatments were (I) control, no bone lesion, (II) metaphyseal femoral bone lesion 3 mm deep and 5 mm diameter and PCL-nHAp implant; (III) lesion but no implant (n=6). Rabbit's clinical evolution was adequate, without affecting gait. No differences in biochemical values (hemograms and transaminases) were detected after 1; 5 and 90 days. Histological studies (90days, 4n) showed that PCL-nHAp scaffold with a corrugated appearance, surrounded, from the outside inwards: A-Hematopoietic bone marrow with megakaryocytes and/or fat with congestive areas; B- few incipiently formed trabeculae, of varied forms; and C- presence of multinucleated giant cells, macrophages, lymphocytes combined with areas of hemorrhage and congestion. An adequate biocompatibility of the scaffolds can be observed, which in its imminent degradation process has not affected the biochemical parameters studied. A non-toxic and biologically active histological response is observed, with moderate levels of inflammation. We believe that longer post-implant periods will allow definitive conclusions.

Vascular calcification in an experimental type 1 Diabetes mellitus model: benefit of naringin treatment

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Vascular calcification (VC) is an important complication of type 1 Diabetes mellitus (DM). Several studies suggest that the antioxidant naringin (NAR) is beneficial for treatment of DM, but its effect on the VC has not been investigated. The aim of this work was to know whether NAR could attenuate the VC in Wistar male rats with DM. Three groups of animals were used: controls, diabetic rats (treated with 60 mg streptozotocin /kg b.w.: STZ), diabetic rats treated with NAR (40 mg/kg b.w.). After 30 days of treatment, plasma was withdrawn and rats were sacrificed to obtain the aortas. Endothelial cells (EC) from aortas were cultured and NO• was measured by the Griess's method. ANOVA and Bonferroni test were used for statistical analysis. NO• production was reduced in STZ rats, which was highly blocked by NAR. In control aortas, estrone (E1) and genistein (Gen) stimulate NO• but in aortas from STZ rats there was lack of NO• stimulation by those hormones. However, NAR restored the capability to stimulate NO• production under E1 and Gen treatments. Isolated aortas from the different groups of animals were exposed to a pro-calcific medium with glycerophosphate for 7 days; the aortas were decalcified and the released calcium was measured by a commercial kit. Calcium content from aortas of STZ rats was 74% higher than that from the control rats. NAR treatment reduced calcium incorporation in aortas from STZ rats to values closed to the control ones. These data were confirmed by AgNO₃ staining. Aortas from STZ rats showed multiple sites of calcification, effect that was abolished by NAR treatment. All data suggest that NAR could prevent damage of the vascular morphology and functionality in DM.

Yerba mate (*Ilex paraguarensis*) consumption is associated with higher total hip mineral density in postmenopausal women: A 3D-Shaper analysis

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We have previously found higher lumbar spine and femoral neck bone mineral density (BMD) in regular mate drinkers. We now report an analysis of the proximal femur with a three-dimensional modeling software (3D-Shaper, Galgo Medical, Barcelona). DXA results (GE Lunar Prodigy) from 90 mate drinkers (MD) and 87 controls (CT) included in the previous study were analyzed with 3D-Shaper to obtain superficial mineral density, trabecular density, and integral density. Data were compared with Student's *t*-test for unpaired data or Mann-Whitney test (as appropriate), and simple and multiple linear regression. Results are mean \pm SD. A $p < 0.05$ was deemed significant. MD and CT showed no differences in age or BMI. Total hip BMD with DXA (g/cm^2) was MD, 0.878 ± 0.113 and CT, 0.791 ± 0.107 ($p < 0.0001$). 3D-Shaper results: Superficial mineral density (mg/cm^2): MD, 145.9 ± 19.5 ; CT, 133.7 ± 18.5 . Trabecular density (mg/cm^3): MD, 151.2 ± 34.4 ; CT 126.4 ± 28.7 . Integral density (mg/cm^3): MD, 297.9 ± 45.4 ; CT, 265.8 ± 41.0 ($p < 0.0001$ for all three variables). Simple linear regression showed a positive BMI effect for the three variables in both groups (p from 0.01 to 0.0002). Age had a negative effect on the three variables in CT, but not in MD. In multiple regression of the total sample ($n=177$) BMI, age and mate consumption significantly influenced ($p < 0.0003$ to < 0.0001) surface density ($r=0.527$), trabecular density ($r=0.545$) and integral density ($r=0.531$). In conclusion, the higher mineral density in total femur in MD is due to both cortical and trabecular bone, with a larger contribution from the latter. Results suggest that mate drinking attenuates the effect of age on proximal femur BMD.